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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/667,859	09/20/2000	Marek Z. Kubin	1010-US	1889

7590 02/27/2002

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EXAMINER
LI, BAO Q

ART UNIT	PAPER NUMBER
1648	7

DATE MAILED: 02/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/667,859	Applicant(s) KUBIN ET AL.	
	Examiner Bao Qun Li	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-72* is/are pending in the application.

4a) Of the above claim(s) *37-47,51-53,58 and 60-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-50,54-57 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *7* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: .

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1648

Election/Restrictions

Applicant's election without traverse of Group III, claims 48-50, 54-57 and 59 in Paper No. 5 is acknowledged.

Applicants are reminded to cancel the claims 37-47, 51-53, 58 and 60-72 drawn to the non-elected groups.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 48-50, 54-57 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 48 is vague and indefinite for using the following indefinite languages to describe the invention:

(1). The word "comprising" used in the claim (a), (b), (c) and (d) is an open language, which fails to identify what the precise structure of the claimed nucleic acid molecule is. If Applicants wish to claim a specific isolated nucleic acid molecule, please amend the claim to a precise sequence structure of the intended molecule.

(2). The word " having" used in the claim (a) and (c) is an open language, which fails to identify what the precise structure of the claimed nucleic acid molecule is. If Applicants wish to claim a specific isolated nucleic acid molecule, please amend the claim to a precise sequence structure of the intended molecule.

(3). The phrase "at least" used in the claim (c) and (d) is an open language, which fails to identify what the precise structure of the claimed nucleic acid molecule is. If Applicants wish to claim a specific isolated nucleic acid molecule, please amend the claim to a precise sequence structure of the intended molecule.

(4). The Identity used in the claim 48 (c) is vague and indefinite because the identity, homology or sequence similarity can be calculated by a variety of different methods, whereby the calculated identity between two sequences will be quite different depending on the algorithm used for calculation. Applicant has referred to various % identities, but there is no indication of the utilized algorithm to calculate the identity sequences in the claim. Furthermore, the calculation of "identity" is affected by variables such as the relative weight given to the sequence gaps versus mismatches, or whether conservative substitutions are weighted differently from non-conservative substitutions. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The above rejections affect the dependent claims 50-54.

Claim 49 is vague and indefinite for using the open languages of " comprising" and "having", which fail to identify what the precise structure of the claimed nucleic acid molecule is as described above. If Applicants wish to claim a particular isolated nucleic acid molecule, please amend the claim to a precise sequence structure of the intended molecule(s). This affects the dependent claim 50-54.

Claims 54 and 59 are unclear for defining what the cited "NAIL polypeptide" is. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Furthermore, please spell out the complete name of "NAIL" polypeptide when it first appears in the claim. This affects the dependent claims 55-56.

Claim 55 is also rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: which "human NAIL polypeptide is genetically engineered to

expressed in the host cell, what kind of conditions is set for promoting the expression and how to purify and identify the "NAIL polypeptide".

Claim Rejections - 35 USC § 112

Claims 48-50, 54-57 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule consisting of SEQ IN NO: 1 and its coding amino acid sequence SEQ ID NO: 2, wherein a fusion proteins made by its amino acid residues 1-221 with tags (SEQ ID Nos: 6-8) exhibit a binding activity to the molecule CD48 and co-stimulatory function in combination with IL-4, CD40L or GM-CSF, does not reasonably provide enablement for any or all molecules having 80% homology isolated by the condition cited in claim 48 or any DNA molecule comprising at least 25 contiguous nucleotide, or other fragment cited in claim 49, wherein all the molecules exhibit to an ability for binding to CD48 or lymphocyte co-stimulatory activities. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and gain in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988).

1) &2) State of art and unpredictability of the field.

The method for isolating and identifying an DNA molecule is well known in the art by using a known DNA probe screening a DNA library at different hybridization condition or by using an antibody to screening a protein expressed by a cDNA library transfected cells followed by isolating the co-responding cDNA. However, it is also a common knowledge for art of molecular cloning that the isolated DNA molecules even with same probe under the same hybridization condition from the same cDNA library can turn out to be structurally and

functionally different molecules. Furthermore, although some molecules exhibit a strong homology between each of the other, they still can be functionally different molecules.

For example, the amino acid sequence of human chemokines, such as MIP-2α, MIP-2β and human GRO/MGSA as disclosed by Robin et al. (The cytokine Factors Book, Academic Press 1994, pp. 189) exhibit high homologies each from other (87%). However, they are identified as totally different molecules because they are originated from different cells and exhibit different functions. For instance, MIP-2 proteins are made by cytokine or LPS- activated monocytes, whereas the GRO/MGSA is made by activated monocytes, fibroblasts, epithelia and endothelia cells. MIP-2 chemokine is a growth factor for myelopietic cells but GRO/MGSA is for fibroblasts and melanoma cells. (See lines 1-19 on page 188). Therefore, using homology, such as 80% to claim all different DNA molecules isolated by a hybridization condition as the same functionally identical molecule is very unpredictable.

This unpredictability is also demonstrated that even one amino acid mutation in a polypeptide can render to be a functionally different molecule and pantenable distinct subject as evidenced by as evidenced by Struffy et al. (Eur. J. Immunol. 1998, Vol. 28, pp. 1262-1271), Proudfoot et al. (US Patent 6,159,711A). Struffy et al demonstrate that a nature form of human chemokine RANTES lacking two N-terminal residue (3-68) lost significantly the chemotactic activity in monocytes and eosinophile in comparison with the full length non-truncated RANTES (Fig. 2 on page 1261). proudfoot et al. et al. teach that the N-terminal modification RANTES with methionine (Meth-RANTES) or Leucin (Leu-RANTES) are turn out to be an antagonist of native RANTES, which exhibit a higher affinity for HIV-1 co-receptor CCR5 than native RANTES for blocking HIV-1 infection (See entire document).

3) Number of working examples and amount of guidance:

Applicants only present in the specification a method for isolating the p38 protein expressing positive clone by using the C1.7 monoclonal antibody and the soluble fusion proteins (SEQ ID NO: 6 and 8) made by amino acid residues from 1-221 are able to bind the CD48 molecule and function as a co-stimulator when in combining with IL4 and GM-CSF.

There is no working examples presented in the specification to illustrate that any or all nucleic acid molecules having 80% homology to the SEQ ID NO: 2 isolated by the hybridization

condition cited in the claim 48 (c) is able to exhibit the same function as the full length of NAIL and the fusion proteins encoded by SEQ ID NO: 6 and 8.

The specification is also deficient for teach which probe to use for isolating any or all molecule, which exhibit more than 80% homology to the SEQ ID NO: 2 or any sequence having more than 25 contiguous nucleotides that is able to exhibit the same function as the SEQ ID NO: 2 , 6 and 8.

Applicants present no guidance for a skilled artisan to use which probe and to look for which 25 contiguous nucleotides to practice successfully the full scope of the claimed invention.

5) Scope of the claims:

The claims are very broad with the claims reciting any or all nucleotide sequence having more than 80% homology or comprising at least 25 contiguous nucleotides insertion to exhibit the same function for binding CD48 molecule and activating or inhibiting cells.

6) Nature of the invention:

The patenable subject matter for the instance application is a structurally and functionally distinct molecule. To enable this, the precise molecular structure being able to exhibit the corresponding and the identical function should be disclosed.

7) Lever of the skill in the art:

Without adequate teaching, a significant hurdles remain to be overcome in order for the skilled artisan to practice successful the claimed invention.

Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-50 and 54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant disclosure, the applicants have only disclosed the sequences identified as NK cell activation inducing ligand (NAIL) encoded by nucleic acid sequence SEQ ID NO: 1, and amino acid sequence SEQ ID NO: 2 as well as the functional soluble extrcellular domain of amino acid residues (1-221) of SEQ ID Nos: 6, 7 and 8 are also disclosed. However, no other sequences, which having at lease 80% homology to SEQ ID NO: 2 or comprising at least 25 contiguous nucleic acids, or other molecules exhibiting the similar function is disclosed.

The specification does not set forth the metes and bounds of that encompasses SEQ ID NO: 1 or 2, because the claim literately use an open language " comprising" or " having" to describe the isolated polynucleotide, there is not enough information about it in literature either to guide the one of ordinary skill in the art to predict the undisclosed at least 80% homology regions where the region may encompass or where the at least 25 contiguous nucleic acid residues are. Therefore, a written description of the other claimed sequences encoding the at lease 80% homology of SEQ ID NO: 2 or comprising 25 contiguous nucleic acids should be disclosed to overcome this rejection. See also *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

The applicant does not have the possession of any other molecules comprising at least 80% homology to SEQ ID NO: 2 and 1 or a fragment having at least 25 contiguous nucleotides to SEQ ID NO-1 or 2 that possess the same function as peptide NAIL peptide of SEQ ID NO. 2, except the extracellular domain fusion proteins of SEQ ID NO: 6-8 disclosed in the Application. Therefore, the claims 48-50 and 54 are rejected under the 35 U.S.C. 112 1st paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48, 50 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Porunellor et al. (J. Immunol. 1993, Vol. 151, pp. 5328-5337).

Porunellor et al. disclose a signal transducer molecule, 2B4, expressed on all NK and T cells that mediate non-MHC-restricted killing. The gene encoding this molecule comprises at least 25 contiguous nucleotide homology with the isolated nucleic acid claimed in the instant application at the position of nucleic acid residue 1295-1320. They also disclose that a mammalian cell COS-7 is transfected to express this molecule and test for the expression of the molecule with a monoclonal antibody against this molecule (See the entire document). Therefore, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-50, 54-57 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valiante et al. (US Patent No. 5,688,690A), Sambrook et al. (Molecular cloning A laboratory Mannual, 2nd edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43-2.84) and Aruffo et al. (Pro. Natl. Aced. Sci. USA, 1987 Vol. 84, No. 23, pages 8573-8577).

Claimed invention is drawn to an isolated polynucleotide encoded by the SEQ ID NO: 1 and its encoding amino acid sequence encoded by the SEQ ID NO: 2. The clone encoded by the

SEQ ID NO: 1 is isolated by using a monoclonal antibody C1.7 (ATCC HB 117170) to screen a cell lines transfected with a human cDNA library prepared from the cytokine stimulated human NK cells, such as IL-2, IL-12, IL-15, INF-γ and anti-CD16. The cDNA encoding a p38 kD protein recognized by the monoclonal antibody C1.7 is isolated and sequenced. The extracellular domain of the said polynucleotide (1-221 amino acid residues) and its full length molecule have been tested to be able to bind the CD48 molecule and exhibit a co-stimulatory function in combining with the IL-4 and GM-CMS to activate the B cell and PBMCs.

Valiante et al. teach that a novel monoclonal antibody (Amb) C1.7 (ATCC HB 117170) is able to recognize an antigen or cellular receptor, which is 38 kD named p38. P38 is expressed in a NK cell and other CD8+ T cell upon activation by cytokines, such as IL2. Valiente also disclose all the function of p38, For example, the activation of p38 by C1.7 on CD8+ T cell mediates a non-MHC-restricted cytotoxicity; stimulates the lymphocyte proliferation, lymphokine production, signal transduction of NK cells and BLT-Esterase release from NK cells (Please see examples 4-10). Valiente et al. also teach several potential utilities for the novel protein p38, such as the use of identifying other ligands, the soluble p38, is possible, may be employed therapeutically to block ligands to CD8 cell to inhibit the CD8 T cell killing of target cells in the situation of a transplantation rejection or autoimmune destruction. The p38 also can be use for stimulating the immune response etc. (see the utilities of p38 disclosed in lines 8 on col. 8 through line 67 on col. 9)

Although Valiante et al. do not disclose the precise DNA and protein sequences of p38; however, they explicitly teach the method for isolating the p38 cDNA or protein sequence. They stated in the Patent that the DNA and protein sequence of p38 can be obtained by resort to conventional methodologies known to one of skill in the art in view of the detail methods taught by Sambrook et al. (Molecular cloning A Laboratory Mannual, 2nd edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43-2.84). They also disclose the explicitly working examples (lines 48 on col. 7 through line line 7 on col. 8 and examples 12 on col. 18 through 19) for isolating the cDNA clone encoding the protein p38 by using Amb C1.7 to screen the protein expression in the cell transfected with the cDNA library and clone the corresponding plasmids, which particularly express the putative p38 cDNA. Upon the identifying the plasmids, the cDNA inserted will be

subcloned and sequenced by the conventional techniques (See Aruffo et al. Pro. Natl. Aced. Sci. USA, 1987 Vol. 84, No. 23, pages 8573-8577).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited reference of Valiante et al. and combine the methods taught by et Valiante et al. Sambrook et al. and Aruffo et al. or any other molecular cloning methods well-known in the art, to manipulate a suitable condition for isolating the p38 molecule and sequence it without unexpected results, whereas the discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 105 USPQ 233. Hence the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li
February 15, 2002

ALI R. SALIMI
PRIMARY EXAMINER